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13. ABSTRACT *(Maximum 200 Words)*

The purpose of this Career Development Award was to expand Dr. Sanderson's current breast cancer research from the effect of intrauterine exposure to estrogen on breast cancer to the interrelationships of prenatal and postnatal growth, hormones, diet and breast cancer. Based on these interrelationships, we hypothesized that insulin resistance will be positively associated with breast cancer. Further, we hypothesized that genetic susceptibility, and adolescent/adult diet and physical activity will modify the effect of insulin resistance on breast cancer. Specific aims were: 1) to undergo intensive training in cancer biology, and nutritional, molecular and genetic epidemiology, 2) to obtain funding to conduct case-control studies of the insulin resistance-breast cancer relationship, and 3) to obtain funding to conduct a cohort study of the association between prenatal and postnatal growth and infant hormone levels.

During the second year of the study, Dr. Sanderson audited Introduction to Genetic and Molecular Epidemiology, conducted analyses of dietary intake and anthropometric measurements from the Shanghai Breast Cancer Study, submitted a preproposal for a HBCU/MI Partnership Award to the Department of Defense to investigate insulin resistance and breast cancer, and participated in the Lower Rio Grande Valley Nutrition Intervention Research Initiative consortium.

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Introduction

The purpose of this Career Development Award was to expand Dr. Sanderson's current breast cancer research from the effect of intrauterine exposure to estrogen on breast cancer to the interrelationships of prenatal and postnatal growth, hormones, diet and breast cancer. Based on these interrelationships, we hypothesized that insulin resistance would be positively associated with breast cancer. Further, we hypothesized that genetic susceptibility, and adolescent/adult diet and physical activity would modify the effect of insulin resistance on breast cancer. Specific aims were: 1) to undergo intensive training in cancer biology, and nutritional, molecular and genetic epidemiology, 2) to obtain funding to conduct case-control studies of the insulin resistance-breast cancer relationship, and 3) to obtain funding to conduct a cohort study of the association between prenatal and postnatal growth and infant hormone levels.

Body

I submitted a new proposal to transfer this Career Development Award from the University of South Carolina to the University of Texas School of Public Health at Brownsville on July 12, 2001. To my knowledge, this transfer is still pending. At the suggestion of my first annual report review, I sent a revised Statement of Work on August 21, 2001 (Appendix A). As a result of my relocation some of the tasks that were planned from months 1-24 will be completed during months 25-48.

During the first year of the study, I completed Task 1.a. by auditing Pathology of Neoplasia with Dr. Kim Creek at the University of South Carolina School of Medicine in Fall 2000. I partially completed Task 1.c. by gaining knowledge of analyses of dietary intake and anthropometric measurements; I co-authored the manuscript "Dietary exposures and oral precancerous lesions in Srikakulam District, Andhra Pradesh, India" and presented the poster "Weight at birth and adolescence and premenopausal breast cancer risk in a low-risk population" at the Society for Epidemiologic Research Meeting in June 2001. I partially completed Task 1.e. by submitting an Idea Award to the Department of Defense entitled "Prenatal and Postnatal Growth, Hormones, Diet and Breast Cancer" in June 2000.

During the second year of the study, the manuscripts on oral precancerous lesions and breast cancer were published (Appendix B). I partially completed Task 1.c. by being added as a co-investigator to the Texas School Physical Activity and Nutrition (SPAN) survey, a statewide assessment of nutritional status and physical activity of elementary, middle and high school students (Appendix C). I partially completed Task 1.e. by submitting a preproposal for a HBCU/MI Partnership Award to the Department of Defense to investigate insulin resistance and breast cancer with investigators from the University of Texas at Brownsville (UTB, Dr. Gerson Peltz, PI) and from the University of Texas School of Public Health (UTSPH, Dr. Maureen Sanderson, PI) (Appendix D). I completed Task 2.a. by auditing Introduction to Genetic and Molecular Epidemiology with Drs. Xigeng Wu, Debbie del Junco and Corinne Aragaki at the University of Texas School of Public Health in Spring 2002 (Appendix E). I partially completed Task 2.c. by presenting the poster on "Adolescent soyfood intake, insulin-like growth factor-I and breast cancer risk" at the Society for Epidemiologic Research Meeting in June 2002 (Appendix F).

During the third year of the study, I will complete Task 1.b. by co-teaching Nutritional Epidemiology with Dr. R. Sue McPherson in Spring 2003. I will complete Task 1.c. by participating in analyses of dietary intake and anthropometric measurements following completion of SPAN data collection, and by conducting analyses of biochemical indicators and breast cancer from a New Mexico study that Dr. McPherson participated in as a co-investigator. I will complete Task 1.d. by working with Dr. McPherson and other members of the Lower Rio Grande Valley Nutrition Intervention Research Initiative (LRGVNIRI) consortium conducting analyses and validating a food frequency questionnaire for use with this population. I will complete Task 1.e. by submitting a full proposal for a HBCU/MI Partnership Award to the Department of Defense to investigate insulin resistance and breast cancer (Appendix G).

During the fourth year of the study, I will complete Task 2.b. by attending the Harvard University summer course in genetic epidemiology taught by Dr. Melissa Austin. I will complete Tasks 2.c. and 2.d. by continuing to investigate adolescent/adult soyfood intake, estrogen, insulin-like growth factor-I, C-peptide and breast cancer risk using the Shanghai Breast Cancer Study. I will complete Task 2.e. by working with the LRGVNIRI consortium to submit a grant to follow a cohort of children from birth through age 12 years to investigate hormone levels in cord blood and subsequent childhood weight, height, diet and physical activity.

Key Research Accomplishments

- Published papers on "Dietary exposures and oral precancerous lesions in Srikakulam District, Andhra Pradesh, India" and "Weight at birth and adolescence and premenopausal breast cancer risk in a low-risk population".

- Partially completed Task 1.c. by being added as a co-investigator to the Texas School Physical Activity and Nutrition (SPAN) survey.

- Partially completed Task 1.e. by submitting a preproposal for a HBCU/MI Partnership Award to the Department of Defense to investigate insulin resistance and breast cancer with investigators from the University of Texas at Brownsville and from the University of Texas School of Public Health.

- Completed Task 2.a. by auditing Introduction to Genetic and Molecular Epidemiology in Spring 2002.

- Partially completed Task 2.c. by presenting the poster on "Adolescent soyfood intake, insulin-like growth factor-I and breast cancer risk" at the Society for Epidemiologic Research Meeting in June 2002.

Reportable Outcomes

1) Manuscripts

Sanderson M, Shu XO, Jin F, Dai Q, Ruan Z, Gao Y-T, Zheng W. Weight at birth and adolescence and premenopausal breast cancer risk in a low-risk population. Br J Cancer 2002;86:84-88.

Hebert JR, Gupta PC, Bhonsle RB, Mehta H, Zheng W, Sanderson M, Teas J. Dietary exposures and oral precancerous lesions in Srikakulam District, Andhra Pradesh, India. Public Health Nutr 2002;5:303-312.

2) Abstracts

Sanderson M, Shu XO, Jin F, Dai Q, Yu H, Gao YT, Zheng W. Adolescent soyfood intake, insulin-like growth factor-I and breast cancer risk. Am J Epidemiol 2002;155:75.

3) Grants

Preproposal Name:	Interrelationships of Hormones, Diet, Body Size and Breast Cancer among Hispanic Women
Funding Agency:	U.S. Army Medical Research and Materiel Command
Period of Funding:	January 1, 2003 – December 31, 2008
Role:	Principal Investigator (20% effort years 1-5, 0% support years 1-2)

Conclusions

To date, my breast cancer research has focused on surrogate markers of intrauterine exposure to estrogen and subsequent breast cancer. This research has led me to the understanding that prenatal and postnatal growth represent critical periods in breast carcinogenesis, in large part due to exposure to estrogen and other hormones/growth factors. Clearly, dietary intake is associated with prenatal and postnatal growth. Diet also has been related to estrogen, insulin-like growth factor-I (IGFI) and other hormones/growth factors, and to breast cancer. Elevated levels of IGFI and insulin, and abdominal obesity are markers for insulin resistance, which has been positively associated with breast cancer in several studies.

This Career Development Award will investigate an area of recent interest in breast cancer, the interrelationships of prenatal and postnatal growth, hormones, diet, and breast cancer. The possibility that insulin resistance may tie these factors together has led to my goal of studying the association between insulin resistance and breast cancer. A secondary goal is to assess the influence of genetic susceptibility, diet and physical activity on this association.

The Lower Rio Grande Valley (LRGV) of Texas is an exceptional location to perform breast cancer research because 85 percent of the population is Hispanic. Hispanic women in the LRGV have a relatively low incidence of breast cancer compared with non-Hispanic white women. In comparison with Hispanic women in the US, Hispanic women residing in the LRGV have a higher mortality from breast cancer. In contrast, Hispanic women are at greater risk of insulin resistance. This research will allow us to investigate whether the reduced risk of breast cancer among Hispanic women in the LRGV may be related to their higher genetic susceptibility to insulin resistance. Women tend to develop insulin resistance if they are genetically susceptible, gain excess weight due to physical inactivity, and consume a high-fat, low-fiber diet during adolescence and adulthood. It is clear that this area of research has promise with regard to explaining the different breast cancer incidence and mortality rates by ethnicity.

In summary, the interrelationships of prenatal and postnatal growth, hormones, diet and breast cancer are complex. There is compelling evidence that insulin resistance may tie these relationships together, and may help explain the elevated risk of breast cancer among certain ethnic groups in the US. Should insulin resistance prove to be associated with breast cancer, the possibility that genetic susceptibility and adolescent/adult diet and physical activity may modify this association will be useful in targeting interventions for women at high risk for breast cancer.

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Sanderson M, Shu XO, Jin F, Dai Q, Ruan Z, Gao Y-T, Zheng W. Weight at birth and adolescence and premenopausal breast cancer risk in a low-risk population. Br J Cancer 2002;86:84-88.

Hebert JR, Gupta PC, Bhonsle RB, Mehta H, Zheng W, Sanderson M, Teas J. Dietary exposures and oral precancerous lesions in Srikakulam District, Andhra Pradesh, India. Public Health Nutr 2002;5:303-312.

Sanderson M, Shu XO, Jin F, Dai Q, Yu H, Gao YT, Zheng W. Adolescent soyfood intake, insulin-like growth factor-I and breast cancer risk. Am J Epidemiol 2002;155:75.

Appendices

Statement of Work

Interrelationships of Prenatal and Postnatal Growth, Hormones, Diet and Breast Cancer

Task 1. Undergo intensive training in cancer biology and nutritional epidemiology, and conduct case-control studies of the insulin resistance-breast cancer relationship, Months 1-24:

a. Audit course in the pathology of neoplasia taught by Dr. Kim Creek
b. Audit course in nutritional epidemiology taught by Dr. R. Sue McPherson
c. In collaboration with Dr. R. Sue McPherson, assess nutritional status and physical activity, and conduct nutritional analyses of dietary intake, biochemical indicators and anthropometric measurements using her ongoing studies at the University of Texas School of Public Health at Houston
d. In collaboration with Dr. R. Sue McPherson, conduct analyses and prepare a manuscript for a validation study of a food frequency questionnaire used in her ongoing studies at the University of Texas School of Public Health at Houston
e. In collaboration with senior colleagues, submit grants to investigate the association between insulin resistance and breast cancer using an ongoing case-control study, the Shanghai Breast Cancer Study (R01-CA64277, PI Zheng) of 1500 cases and 1500 controls

Task 2. Undergo intensive training in molecular and genetic epidemiology, and conduct a cohort study of the association between prenatal and postnatal growth and infant hormone levels, Months 25-48:

a. Audit course in molecular epidemiology taught by Dr. Corinne Aragaki
b. Attend the Harvard University summer course in genetic epidemiology taught by Dr. Melissa Austin
c. In collaboration with Dr. Xiao Ou Shu, conduct analyses and prepare a manuscript investigating whether adolescent/adult diet and physical activity modifies the effect of estrogen and insulin-like growth factor 1 (IGF1) on breast cancer using a recently funded ancillary study from the Shanghai Breast Cancer Study
d. In collaboration with Dr. Wei Zheng, conduct analyses and prepare a manuscript investigating whether genetic susceptibility and adolescent/adult diet and physical activity modify the effect of estrogen, IGF1, insulin and C-peptide on breast cancer among women in Shanghai
e. In collaboration with senior colleagues, submit a grant to conduct a cohort study of 800 mothers and their female infants to investigate the association between maternal age, diet, preeclampsia, and infant birth weight, and hormone levels using the infants' cord blood; children will be followed for 12 years and childhood/adolescent weight, height, diet and physical activity will be assessed at 4-year intervals

Appendix B

British Journal of Cancer (2002) 86, 84–88

www.bjcancer.com

Weight at birth and adolescence and premenopausal breast cancer risk in a low-risk population

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[1]University of Texas School of Public Health at Brownsville, University of Texas Brownsville, 80 Fort Brown, Brownsville, Texas, TX 78520, USA; [2]Center for Health Services Research and Vanderbilt-Ingram Cancer Center, Vanderbilt University, Nashville, Tennessee, TN 37232-8300, USA; [3]Department of Epidemiology, Shanghai Cancer Institute, Shanghai, People's Republic of China

We assessed breast cancer risk in relation to weight at birth and adolescence. In-person interviews were completed with the biological mothers of women aged 45 years and younger who participated in the Shanghai Breast Cancer Study in 1996–98 (288 cases, 350 controls). After adjustment for confounding, women who were 4000 g or more at birth were not at increased risk of breast cancer (odds ratio=0.7; 95% confidence interval 0.4–1.4) relative to women whose birth weight was 2500–2999 g. Compared with women of average perceived weight at age 15 years, no relation was apparent for heavier than average weight based on maternal report (odds ratio=0.7; 95% confidence interval 0.5–1.2) or self-report (odds ratio=1.0; 95% confidence interval 0.7–1.6). Perceived adolescent weight and height did not modify the association of birth weight with breast cancer risk. These results suggest that weight early in life is not related to premenopausal breast cancer risk in this low-risk population.
British Journal of Cancer (2002) **86,** 84–88. DOI: 10.1038/sj/bjc/6600009 www.bjcancer.com

Keywords: breast cancer; birth weight; adolescent weight; adult body size

Epidemiology

Premenopausal breast cancer has been linked to high birth weight (Ekbom *et al*, 1992; Innes *et al*, 2000; Michels *et al*, 1996; Sanderson *et al*, 1996). Conversely, high adolescent (Coates *et al*, 1999; Hislop *et al*, 1986; Le Marchand *et al*, 1988a), early adult (Coates *et al*, 1999; Huang *et al*, 1997; Trentham-Dietz *et al*, 1997) and adult weight or body mass index (Brinton and Swanson, 1992; Huang *et al*, 1997; Swanson *et al*, 1996; Ursin *et al*, 1995; van den Brandt *et al*, 2000) appear to be protective against premenopausal breast cancer. Several studies have investigated the association between breast cancer and weight at birth (De Stavola *et al*, 2000; Ekbom *et al*, 1992, 1997; Innes *et al*, 2000; Le Marchand *et al*, 1988b; Michels *et al*, 1996; Sanderson *et al*, 1996, 1998a) or weight at adolescence (Brinton and Swanson, 1992; Choi *et al*, 1978; Coates *et al*, 1999; Franceschi *et al*, 1996; Hislop *et al*, 1986; Le Marchand *et al*, 1988a; Pryor *et al*, 1989) with inconsistent findings. Possible limitations of these studies related to exposure measurement and age at diagnosis of breast cancer.

Since self-report of body size in early life is prone to misclassification, maternal report may be less subjective. Maternal report was available for two of the studies investigating breast cancer risk associated with birth weight (Michels *et al*, 1996; Sanderson *et al*, 1998a), but none of the studies of adolescent weight. The present analysis was conducted to assess whether birth weight and adolescent weight as reported by subjects' mothers were related to premenopausal breast cancer risk. In addition, we investigated whether perceived adolescent weight and height modified the association of birth weight with breast cancer risk.

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MATERIALS AND METHODS

Detailed methods of this population-based case–control study appear elsewhere (Gao *et al*, 2000). Briefly, all women aged 25–64 years who were permanent residents of urban Shanghai at the time of diagnosis of first primary invasive breast cancer (August 1996 through March 1998) were eligible for the study. Two senior pathologists histologically confirmed all diagnoses. We used rapid case ascertainment supplemented by the Shanghai Cancer Registry to identify breast cancer cases who had no prior history of cancer. A total of 1459 breast cancer cases (91.1% of eligible cases) completed a standardized in-person interview. Of potentially eligible cases, 109 refused (6.8%), 17 died prior to the interview (1.1%), and 17 were not located (1.1%).

The Shanghai Resident Registry, a listing of all permanent adult residents of urban Shanghai, was used to randomly select controls. Controls were frequency matched to cases on age (5-year interval) based on the number of incident breast cancer cases by age group reported to the Shanghai Cancer Registry from 1990 through 1993. Women who did not reside at the registered address at the time of the study were ineligible. A total of 1556 controls (90.4% of eligible controls) completed a standardized in-person interview. The remaining 166 potentially eligible controls (9.6%) refused to participate. Two women died prior to the interview and were excluded.

The study was approved by relevant institutional review boards in Shanghai and the United States. Women were interviewed at hospitals (cases) or at home (cases and controls) by trained interviewers. The subject questionnaire collected information on demographic factors, reproductive and medical histories, family history of cancer, use of oral contraceptives and hormone replacement therapy, diet, physical activity, lifestyle factors, and adolescent and adult body size. Women were asked how their perceived weight and height compared with their peers at the ages of 10,

suspected effect modifiers of these relations. An additional strength of the study was the good agreement between maternal and subject reporting of adolescent body size. There are, however, some measurement errors, which may have attenuated the estimated odds ratios is this study.

In summary, our study indicates that weight at birth and adolescence has little influence on breast cancer risk in Chinese women. These results suggest that weight early in life is not related to premenopausal breast cancer risk in this low-risk population. Future studies should assess these relations to clarify the role that weight early in life may play in breast cancer risk.

ACKNOWLEDGEMENTS

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Table 4 Odds ratios of breast cancer associated with joint effects of birth weight, adolescent weight and adolescent height

		Birth weight					
		<3500 g			⩾3500 g		
		Case/Ctrl	OR[a]	(95% CI)	Case/Ctrl	OR[a]	(95% CI)
Maternal perceptions							
Weight at 15 years	Height at 15 years						
⩽Average	⩽Average	141/150	1.0	(Referrent)	28/45	0.7	(0.4–1.1)
	>Average	32/38	0.8	(0.5–1.4)	18/21	1.0	(0.5–1.9)
>Average	⩽Average	14/27	0.6	(0.3–1.1)	3/9	0.3	(0.1–1.2)
	>Average	7/8	0.9	(0.3–2.5)	4/7	0.6	(0.2–2.1)
Subject perceptions							
Weight at 15 years	Height at 15 years						
⩽Average	⩽Average	136/148	1.0	(Referrent)	20/46	0.4	(0.2–0.8)
	>Average	37/48	0.8	(0.5–1.3)	21/24	1.0	(0.5–1.9)
>Average	⩽Average	13/17	0.9	(0.4–2.0)	6/8	0.8	(0.3–2.3)
	>Average	8/10	0.8	(0.3–2.1)	5/4	1.6	(0.4–6.7)

[a]Adjusted for age, income, family history breast cancer in first-degree relative, history of fibroadenoma, age at menarche, parity, and age at first live birth.

Epidemiology

was more pronounced among women who were heavier than average during adolescence and whose adult body mass index was at or above the median (OR=0.31, 95% CI 0.16–0.60). In the present analysis, no relation was apparent for breast cancer associated with heavier than average perceived weight at the age of 15 based on maternal report or self-report. Neither adult body mass index nor waist-to-hip ratio modified the effect of perceived adolescent weight on breast cancer risk.

The biological mechanism that Stoll (1998) proposed to help explain the reduced risk of premenopausal breast cancer associated with adolescent obesity in some studies was that obesity triggered a hyperinsulinemic insulin resistance at puberty that could lead to abnormal ovarian steroidogenesis and anovulation. Most of the women in this study grew up during a period when food and meat were rationed and adolescent obesity was rare, thus perceived weight at the age of 15 may not reflect adolescent obesity as defined among Western women. Spearman correlation coefficients were calculated to assess whether age at menarche, used as a marker of adolescence, was correlated with perceived weight or height at the age of 15. Whether reported by the subject or her mother, these correlations were negative and clustered around zero.

In a previous analysis of this study, premenopausal breast cancer was unrelated to early adult and adult weight, but was associated with a high adult waist-to-hip ratio, even after adjustment for body mass index (Shu *et al*, 2001). These findings differ from the majority of studies of this topic conducted among Western women. As was the case for early adult and adult weight, an alternative explanation for the null associations found for weight at birth and adolescence and breast cancer risk is the paucity of women at the extremes of these measures.

Our findings of increased risks of premenopausal breast cancer associated with maternal report and combined maternal and subject report of perceived height as shorter than average at the age of 15 differs from all previous studies. Coates *et al.* (1999) reported reduced risks for women who were much shorter than average at the ages of 15 to 16. Brinton and Swanson (1992) reported an increased premenopausal breast cancer risk associated with taller than average perceived height at the age of 16. An earlier adolescent growth spurt and tallness in childhood has been linked to earlier menarche (Preece, 1989), an established breast cancer risk factor. In the present study, the mean menarcheal age was approximately 14.5 years, which was nearly 2 years later than the mean age among US women at the time the majority of women in this study were achieving menarche (Zacharias *et al*, 1976). The later age at menarche experienced by women in China meant that some of the women in the present analysis had not undergone their adolescent growth spurt by the age of 15, which may partially explain the lack of a positive association observed in this study with taller adolescent height.

One previous study has investigated the joint effect of birth weight and adolescent weight or adolescent height on breast cancer risk. De Stavola *et al.* (2000) recently examined the effects of birth weight and childhood growth on subsequent breast cancer risk in a cohort study in the UK. They reported a borderline increase in risk of premenopausal breast cancer associated with a birth weight of 3500 g or more (relative risk [RR]=2.31, 95% CI 0.93–5.74). This risk was modified by height at the age of 7, with no association among women who were short or average (RR=1.23, 95% CI 0.31–4.91) and a pronounced elevation in risk among women who were tall (RR=5.86, 95% CI 1.97–17.44). They concluded that the birth weight and breast cancer relation might be mediated through childhood growth. Height at the age of 7 was chosen to reflect pre-pubertal growth, but there was no significant interaction for the height at the age of 15. In the present analysis, perceived height at the age of 10 (data not shown) and the age of 15 did not modify the effect of birth weight on breast cancer risk. However, women who were 3500 g or more and short or average height at the age of 15 were at decreased risk of breast cancer.

There were several limitations of this study. Data on birth weight and maternal perception of adolescent body size analyses were available only in a subgroup of premenopausal women, reducing statistical power to detect effect modification. The narrow distribution of weights at birth and adolescence in China (Eveleth and Tanner, 1976; Fung *et al*, 1989) may have further limited the statistical power to evaluate the association of these variables with breast cancer risk. Reporting of birth weight and perceptions of weight and height during adolescence are prone to misclassification. However, in a study conducted in Washington State, we found very high correlations between maternal reporting and birth certificate recording of birth weight (case mothers r=0.89, control mothers r=0.84) (Sanderson *et al*, 1998b). To our knowledge, no validation studies of maternal reporting of adolescent body size have been conducted.

This study has many strengths. The population-based nature of the study and its high response rates among subjects (cases: 91%; controls: 90%) and their mothers (case mothers: 80%; control mothers: 82%) minimizes selection bias. We adjusted for known breast cancer risk factors, and evaluated the weight at birth and adolescence and breast cancer associations in conjunction with

The risks for breast cancer associated with maternal and subject perceptions of subjects' weight and height at the age of 15 separately and combined are shown in Table 3. For mothers and subjects whose perceptions differed we created a fourth category. Compared with women of average perceived weight at the age of 15, no relation was apparent for heavier than average weight based on maternal report (OR=0.7; 95% CI 0.4–1.1) or self-report/combined maternal and subject report (OR=1.1; 95% CI 0.6–2.2). Elevated risks of breast cancer were seen for women whose mothers perceived they were shorter than average at age 15 (OR=2.1, 95% CI 1.3–3.5), which was reflected in the combined maternal and subject estimate (OR=1.9, 95% CI 1.0–3.7). We calculated Spearman correlation coefficients to assess the reliability of reporting of perceptions of weight and height by case–control status (Armstrong *et al*, 1992). The correlations comparing maternal and subject perceptions were reasonably consistent (weight r=0.46, height r=0.59).

Table 4 shows the joint effect of birth weight, adolescent weight, and adolescent height on breast cancer risk. The referent group is women who were less than 3500 g at birth, and who at the age of 15 were of average weight and average height. Perceived adolescent weight and height did not modify the effect of birth weight on breast cancer risk or vice versa. Women whose birth weight was 3500 g or more and who perceived themselves to be of low or average adolescent weight and low or average adolescent height were at reduced risk of breast cancer (OR=0.4, 95% CI 0.2–0.8). Neither adult body mass index nor waist-to-hip ratio modified the effect of birth weight or adolescent weight on breast cancer risk (data not shown).

DISCUSSION

We found no association between high birth weight and premenopausal breast cancer, in agreement with some (De Stavola *et al*, 2000; Ekbom *et al*, 1997; Le Marchand *et al*, 1988b; Sanderson *et al*, 1998a), but not all (Ekbom *et al*, 1992; Innes *et al*, 2000; Michels *et al*, 1996; Sanderson *et al*, 1996), of the previous studies of this topic. Trichopoulos (1990) hypothesized that exposure to high levels of endogenous estrogen *in utero* may be a possible risk factor for subsequent breast cancer. In a study conducted in Greece, high birth weight was associated with high pregnancy estrogen levels (Petridou *et al*, 1990). However, Lipworth *et al.* (1999) reported substantially higher mean levels of pregnancy estrogens and significantly lower mean birth weights among women in Shanghai than among their counterparts in Boston. They speculated that higher albumin and sex hormone binding globulin among Chinese women could decrease the bioavailability of oestrogens. This may partially explain the lack of a positive association with high birth weight observed in the present analysis.

The results of studies on adolescent weight and premenopausal breast cancer risk are inconsistent. Premenopausal breast cancer risk associated with heavier than average weight at the age of 15 or thereabouts was decreased in some studies (Coates *et al*, 1999; Hislop *et al*, 1986; Le Marchand *et al*, 1988a), increased in one study (Pryor *et al*, 1989), and had no association in other studies (Brinton and Swanson, 1992; Choi *et al*, 1978; Franceschi *et al*, 1996). The reduction in risk reported by Le Marchand *et al.* (1988a) was for the highest tertile of body mass index compared with the lowest tertile (OR=0.45, 95% CI 0.23–0.86). This relation

Table 3 Odds ratios of breast cancer associated with perceptions of adolescent body size

	Cases (n=288)	Controls (n=350)	OR[a]	(95% CI)
		Maternal perceptions		
Perceived weight at age 15 years[b]				
<Average	67	75	1.2	(0.8–1.7)
Average	186	219	1.0	(Referent)
>Average	34	56	0.7	(0.4–1.1)
Perceived height at age 15 years[c]				
<Average	46	34	2.1	(1.3–3.5)
Average	164	236	1.0	(Referent)
>Average	77	80	1.4	(0.9–2.0)
		Subject perceptions		
Perceived weight at age 15 years[b]				
<Average	101	132	1.0	(0.7–1.4)
Average	144	169	1.0	(Referent)
>Average	42	49	1.1	(0.7–1.7)
Perceived height at age 15 years[c]				
<Average	47	61	1.1	(0.7–1.7)
Average	156	194	1.0	(Referent)
>Average	85	95	1.2	(0.8–1.7)
		Maternal and subject perceptions combined		
Perceived weight at age 15 years[b]				
<Average	51	55	1.1	(0.7–1.8)
Average	118	128	1.0	(Referent)
>Average	20	22	1.1	(0.6–2.2)
Did not agree	98	145	0.8	(0.5–1.1)
Perceived height at age 15 years[c]				
<Average	25	21	1.9	(1.0–3.7)
Average	120	161	1.0	(Referent)
>Average	58	58	1.4	(0.9–2.2)
Did not agree	85	110	0.9	(0.7–1.5)

[a]Adjusted for age, income, family history of breast cancer in first-degree relative, history of fibroadenoma, age at menarche, parity, and age at first live birth. [b]Additionally adjusted for perceived height at specific age. [c]Additionally adjusted for perceived weight at specific age.

15 and 20. After completing the interview, women were weighed and had their standing and sitting height, and waist and hip circumferences measured. Information on exposures pertained to the period before an assigned reference date, the diagnosis date for breast cancer cases and a similar date for controls.

The biological mothers of women the age of 45 and younger who resided in Shanghai provided detailed information about the subject's adolescent diet and body size, and about her pregnancy with the subject. In-person interviews were completed with the mothers of 296 cases and 359 controls (with respective response rates of 79.6 and 81.8%). Eight cases and nine controls were subsequently excluded because they were postmenopausal, resulting in 288 cases and 350 controls for this analysis.

We used unconditional logistic regression to estimate the relative risk of breast cancer associated with weight at birth and adolescence while controlling for confounders (Breslow and Day, 1980). All variables were entered into models as dummy variables. In multiple logistic regression models, we assessed linear trend by treating categorical variables as continuous variables.

RESULTS

Table 1 compares known breast cancer risk factors of cases and controls. Compared to controls breast cancer cases were slightly older, had a lower income, and were more likely to have a history of fibroadenoma, a higher waist-to-hip ratio, and a later age at first birth. For consistency with most previous studies, subsequent analyses were adjusted for family history of breast cancer, menarcheal age, parity, and all of the preceding variables, except waist-to-hip ratio. Since adult waist-to-hip ratio may be in the causal pathway between birth and adolescent weight and breast cancer, it and adult body mass index were assessed as effect modifiers rather than as confounders. Further adjustment of birth weight for other perinatal factors did not materially change the odds ratios. Perceived weight is adjusted for perceived height at specific ages and vice versa.

Table 2 presents the odds ratios (ORs) and 95% confidence intervals (CIs) for breast cancer associated with maternal report of birth weight. After adjustment for confounding factors, women who were 4000 g or more at birth were not at increased risk of breast cancer (OR=0.7; 95% CI 0.4–1.4) relative to women whose birth weight was 2500–2999 g. When we dichotomized birth weight an identical odds ratio for women whose birth weight was 3500 g or more (OR=0.7, 95% CI 0.5–1.1) was found, compared with women who were less than 3500 g.

Table 2 Odds ratios of breast cancer associated with maternal report of birth weight

	Cases (*n*=288)	Controls (*n*=350)	OR[a]	(95% CI)
Birth weight (grams)				
<2500	14	18	0.9	(0.4–2.0)
2500–2999	58	70	1.0	(referrent)
3000–3499	122	135	1.1	(0.7–1.6)
3500–3999	35	53	0.8	(0.4–1.4)
⩾4000	18	29	0.7	(0.4–1.4)
P trend[b]			*P*=0.32	

[a]Adjusted for age, income, family history of breast cancer in first-degree relative, history of fibroadenoma, age at menarche, parity, and age at first live birth. [b]Excluding women less than 2500 g.

Table 1 Comparison of cases and controls for selected risk factors

	Cases[a] (*n*=288)	Controls[a] (*n*=350)	*P*-value
Age	39.6±3.4	38.6±3.9	<0.01
Education (%)			
Elementary education	1.0	0.0	
Middle+high school	91.7	90.9	
Profession, college and above	7.3	9.1	0.12
Per capita income (Yuan) (%)			
<4000	17.0	15.7	
4000–5999	48.6	37.7	
6000–7999	6.9	10.9	
8000–8999	14.6	24.6	
⩾9000	12.9	11.1	<0.01
Breast cancer in first degree relatives (%)	1.7	2.6	0.47
Ever had breast fibroadenoma (%)	11.5	5.4	<0.01
Regular alcohol drinker (%)	3.5	3.1	0.82
Ever used oral contraceptives (%)	6.6	7.4	0.68
Exercised regularly (%)	11.1	14.3	0.23
Body mass index	22.5±3.1	22.3±3.1	0.36
Waist-to-hip ratio	0.80±0.06	0.78±0.06	<0.01
Nulliparous (%)	6.6	5.1	0.43
Number of live births[b]	1.0±0.19	1.0±0.17	0.98
Age at first live birth[b] (years)	28.0±3.3	27.5±2.8	0.03
Months of breast feeding[c]	5.3±4.9	5.4±4.9	0.79
Menarcheal age (years)	14.3±1.5	14.4±1.6	0.45
Height (cm)	160.0±5.1	159.9±5.3	0.76
Weight (kg)	57.7±8.8	56.9±8.5	0.30

Subjects with missing values were excluded from the analysis. [a]Unless otherwise specified, mean±s.d. are presented. [b]Among women who had live births. [c]Among women who ever breast fed.

Epidemiology

Appendix C

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Dietary exposures and oral precancerous lesions in Srikakulam District, Andhra Pradesh, India

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Abstract

Objective: To test the effect of dietary nutrients on oral precancerous lesions in a reverse-smoking (i.e. smoking with the glowing end inside the mouth) population in South India.

Design: Case–control. Cases with precancerous lesions were matched to an equal number of lesion-free controls matched on age (±5 years), sex and village. All subjects used tobacco in some form. Dietary data were obtained using an interviewer-administered food-frequency questionnaire, designed for use in this population. All interviews were conducted blinded to the disease status of the subject. Data were analysed using logistic regression.

Setting: Nineteen rural villages in Srikakulam District, Andhra Pradesh.

Subjects: From a survey of 6007 tobacco users, 485 (79% women) were found to have precancerous, mostly palatal, lesions (cases), and 487 lesion-free subjects were selected as controls.

Results: All eligible subjects consented to participate and nearly all (>99%) had complete data for analyses. Reverse smoking was the most common form of tobacco use among cases (81.9%) and controls (73.5%), and reverse smokers were 5.19 times more likely than chewers to have these lesions (95% confidence interval = 1.35, 19.9). After controlling for relevant covariates, including the type of tobacco use, protective linear effects were observed for zinc (70% reduction across the interquartile range, $P < 0.002$), calcium (34% reduction, $P < 0.002$), fibre (30% reduction, $P < 0.009$), riboflavin (22% reduction, $P < 0.03$) and iron (17% reduction, $P < 0.05$).

Conclusions: Several dietary nutrients appear to protect against oral precancerous lesions that are strongly associated with reverse smoking. The results of this study indicate scope for targeting dietary factors in preventing oral cancer, which should be coupled with aggressive anti-tobacco use efforts.

Keywords
India
Oral neoplasms
Precancerous conditions
Dietary nutrients

Oral cancer is the sixth commonest cancer in the world[1]. Its incidence is particularly high in India, some other countries in Asia, and in certain places in the Western hemisphere, e.g. parts of France and Brazil, where smoking and alcohol drinking are major risk factors. In India, chewing and smoking of tobacco products in various forms is primarily responsible for the high incidence. The World Health Organization (WHO) has estimated that 90% of oral cancers in India among men were attributable to chewing and smoking habits[2]. In previous work, it has been shown that reverse smoking (i.e. with the glowing end inside the mouth), a practice common among women in a coastal region of Andhra Pradesh in east–central India, is strongly associated with oral, particularly palatal, precancerous lesions that may progress to carcinoma and may exhibit epithelial atypia of the palate[3–5].

Nutritional risk factors also have been implicated in cancers of the oral cavity. A number of studies have indicated that the consumption of various vegetables and fruits reduces risk. These relationships may be independent of other risk factors and show a dose–response effect[6–10]. However, any cancer of the alimentary tract can

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affect dietary intake, which in turn may affect the accuracy of assessment of usual dietary habits among cases[11].

Within the oral cavity, cancer generally develops on the tongue, buccal mucosa, gingiva, lips, floor of the mouth, but less often on the palate, except in reverse smokers among whom it is the most common location. In the region of this study, Srikakulam District, Andhra Pradesh, reverse smoking is practised using *chutta*, a coarsely made cheroot (cigar with both ends open) about 5–12 cm long[5]. The prevalence and incidence of these precancerous palatal and other mucosal changes are very high among such reverse smokers[12].

Oral, including palatal, cancer often is preceded by precancerous lesions[13]. The relative risk of developing oral cancer among individuals with oral precancerous lesions has been found to be very high (i.e. >200), demonstrating the fact that such lesions lie on the causal pathway to cancer[14]. The association of oral precancerous lesions with tobacco habits follows a pattern similar to that of oral cancer[12]. Because the prevalence of oral precancerous lesions is much higher than that of oral cancer, these conditions provide a useful clinical marker for oral cancer. For this reason, they have been used as such in large-scale intervention trials[15]. In addition to improving the outcome yield of such studies, using precancerous lesions provides an opportunity to avoid some of the biases associated with measuring dietary intake in individuals with oral cancer. Clearly, the high rate of oral cancer underlines this as a matter of great public concern and the presence of a precancerous marker lesion makes careful epidemiological study more feasible. A probable wide range of variability in nutrient exposures[16–18] that could overcome a common problem with limitations in the distribution of nutrient intake[19] provided an additional rationale for evaluating dietary factors for oral cancer precursors in India.

The primary goal of this research was to test the relationship between the presence of precancerous changes in the mouth and the dietary intake of: the antioxidants, β-carotene and ascorbic acid; the B vitamins, thiamine and riboflavin; and the trace elements, iron, copper, calcium and zinc. These micronutrients were chosen on the basis of a variety of laboratory studies[20,21], human experimental studies[22–26], observational studies[27–30] and the availability of data in the nutrient database[31].

Methods

Subject recruitment/data collection

This population-based case–control study was conducted in 19 villages not included in earlier studies in Srikakulam District, Andhra Pradesh[12,32]. A preliminary census was conducted for listing households along with the identification information for each member of the household and their tobacco use status.

A team consisting of dentists, field investigators and a social scientist especially trained in conducting diet–nutrition interviews visited each household on the house lists with the aim of examining all tobacco users aged 15 years and over. As the first step in the recruitment/data collection process, a field investigator interviewed the potential study subject and filled out a questionnaire containing basic demographic information and details of tobacco and alcohol habits. An experienced dentist then examined the subject for the presence of oral precancerous lesions. The subject was then classified as a case if she or he had an eligible precancerous lesion (palatal changes consisting of patches and red areas, leukoplakia, erythroplakia, submucous fibrosis, and an ulcer or a growth suspicious of oral cancer). In the initial survey, 6007 tobacco users were examined. Of these, 485 were found to have one or more lesions necessary to qualify them as a case. The potential control pool consisted of all examined persons who were found to be free of lesions. A control ($n = 487$) was identified as the next available examinee found to be free of lesions, and matched on sex, age (±5 years) and village. Because of the design of the study all cases and controls used tobacco in some form. Therefore, type of tobacco habit (yes/no for each category, chewing, smoking, reverse smoking) was recorded and used as a control variable in all statistical analyses. All selected cases and controls consented to participate in the study.

An 80-item food-frequency questionnaire (FFQ) specific to this population was developed with an aim of estimating nutrient intake. This was similar to instruments developed for use in Kerala[33] and Gujarat[34]. The FFQ interview for the case–control study was conducted only if a subject was selected to participate and after obtaining informed consent. To minimise the likelihood of bias, all data were collected in a blinded fashion (i.e. the interviewer was not aware of the status of the subject and the subject was not told of the presence or absence of the lesion until completion of the interview, within 5 days of the exam). Therefore, unlike in most case–control studies, the FFQ was administered without anyone involved in the collection of the dietary data having knowledge of the subject's disease status.

The FFQ took approximately 25 minutes to complete. It consisted of questions on the typical frequency and quantity of consumption of 80 food items representing >95% of exposure to total energy, fat, fibre, iron, copper, zinc, calcium, ascorbic acid, β-carotene and the B vitamins in this population.

FFQ validation

The FFQ specifically developed for use in this population was validated for collecting dietary information and estimating nutrient intake. The nutrient database[31] was the same as used in previous work by our group[33,34]. Some 60 people (30 male/female pairs) living in the broad area

of this study, but not in the villages sampled for the case–control study, were selected for the validation study (i.e. it was an external validation study). On eight randomly selected days over the year, subjects were administered 24-hour diet recall interviews (24HR). The FFQ was administered twice, exactly a year apart. A brief description of the results of the comparison between the FFQ- and 24HR-derived nutrient values is included in this paper.

Oral precancerous lesions

Palatal changes constitute the most important precancerous changes among reverse *chutta* smokers, the most common form of tobacco use in this region. Two components of these palatal changes, namely patches and red areas, were included in this study. Patches were defined as well-demarcated, slightly elevated plaques, which qualify for the clinical term leukoplakia[4]. Red area was defined as palatal mucosa showing well-defined reddening without ulceration[4]. Other non-palatal lesions included in this study were leukoplakia classified into homogeneous, nodular and ulcerated (for a detailed description see Pindborg[13]) and oral submucous fibrosis. In two females, lesions suspicious of being oral cancer were confirmed as such on histopathological examination and referred for care. It is important to note that both heat from reverse smoking and products of tobacco combustion play important roles in carcinogenesis, although it is not feasible to delineate the effect of each[12,15].

Tobacco habits

Reverse *chutta* smoking was the common form of smoking in this region[5], especially among women; 98% of women tobacco users engaged in this practice. In this study, overall, a minority of individuals smoked *bidis* (2.6%), cigarettes (1.7%) and *chutta* in the conventional manner (14.3%), or chewed tobacco (2.2%). *Chutta* is a coarsely prepared cheroot. *Bidi* is a smoking stick prepared by rolling 0.15–0.25 g of sun-dried flake-form of tobacco in a rectangular dried piece of *temburni* leaf (*Diospyrous melanoxylon*). Details of these and other forms of tobacco habits in India are described elsewhere[35].

Statistical methods

For the external validation study, nutrient scores derived from the FFQ were compared with those derived from the eight 24HR administered on randomly selected days over the one-year study period. Pearson product moment and Spearman rank order correlations were used as the criteria for comparison.

Descriptive statistics were computed overall and separately for cases and controls. These consisted of either standard parametric statistics for continuous variables (e.g. the nutrient scores) or non-parametric frequency statistics for all variables measured on an ordinal or nominal scale or as counts. The 25th, 50th and 75th percentile values for each of the nutrient scores were computed based on the entire dataset. Multivariable analysis was conducted using logistic regression. Because of the strength of association between specific types of tobacco use and oral cancer and precancer, some designation of tobacco habit was considered in specifying all statistical models. Two indicator variables describing the three major categories of tobacco use in this population (reverse *chutta* smoking, smoking in the conventional manner and chewing tobacco in any form (referent group)) was conceptually the simplest scheme and had the largest explanatory ability of any alternative. Duration of use was closely associated with age and no measure of intensity appeared to affect estimates of risk after accounting for type of tobacco use.

Social and economic variables often serve as proxies for potentially important risk factors for cancer and therefore are frequently included in analyses. As the vast majority (93%) of the population was illiterate, it was not possible to use education, one of our two indicators, in analyses. For reasons of multicollinearity, it also was not possible to include economic status (described as either higher – a brick house with tiled or corrugated tin roof; or lower – a mud house with thatched roof) because it was strongly related to smoking; e.g. for overall smoking (including reverse smoking) the Mantel Haenzel chi-square was 4.24 ($P = 0.04$), whereas for conventional smoking the chi-square was 52.36 ($P < 0.0001$). Nutrient scores were included both as continuous variables and quartiles, in separate models, because dietary nutrients are highly correlated with one another. Because dietary exposure estimates may be biased by overall errors in reporting[36,37] and some nutrients have a stoichiometric relation with total energy utilisation[38], we controlled for total energy intake by fitting it as a covariant in each model. For nutrients evincing linear effects, we computed the effect across the interquartile range of its distribution, thus standardising the effect for the distributions of nutrient exposure reported in this population.

The primary analyses were conducted on the main study data for all types of lesions combined. Additional analyses were conducted by gender and by lesion type. All analyses were conducted using the personal computer version of SAS[39,40].

Follow-up study

After one year, all 6007 tobacco users were re-examined. Among those found to be lesion-free at the first survey, 39 had a new incident lesion. For each case thus identified, a control was selected. These data were analysed separately in the same manner as for the main case–control study dataset. In order to assess whether the expected wide confidence interval (CI) was simply due to sample size (and not other factors affecting precision), we adjusted the 95% CI for the ratio of the sample sizes of the prevalent and incident case series. The 'sample-size-adjusted' 95% CI

is obtained by the formula antilog $[b \pm 1.96\mathrm{SE}_b/\sqrt{n_p/n_i}]$, where b = log odds ratio, SE_b = standard error of b, n_p = number of prevalent cases and n_i = number of incident cases.

Results

Table 1 shows the results from the external validation study. These consist of correlation coefficients for each of the nutrients of interest plus total energy intake, a control variable fit in all logistic regression models. Correlation coefficients for total fat and fat as percentage of energy also are shown. With the exception of sodium, ascorbic acid and β-carotene, the correlation coefficients were moderately high, comparing very favourably with those of other studies[41].

The descriptive statistics of the study population, including the reported daily nutrient intakes as estimated by the FFQ, are shown in Table 2. In both the validation study and the case–control study, there was an apparent miscalibration for rice preparations (rice, rice with starch water, and rice with buttermilk). These preparations represented 78% of total caloric intake reported in this population; about three times higher than expected based on estimates from other rice-eating populations[16] including a group we had studied in Kerala[33]. As presented, energy intake represents the total from the remaining 77 foods, but with a re-calibration of rice intake based on measurements from the predominantly rice-eating study population in Kerala[33]. This was done by computing the metabolic need per kg body weight by sex in Kerala (i.e. kcal kg^{-1} day^{-1}) and applying that rate to an individual's consumption of rice in *this* population. In all analyses of study data, the intake of energy actually reported (and not the adjusted value shown in the table) was used as a control variable. This was done to avoid using imputed data in the regression analyses.

Due to miscalibration of rice intake, the intake of many nutrients was overestimated because of the amounts involved (even though rice normally is only a minor

Table 1 Results of correlation analyses – Food-Frequency Questionnaire External Validation Study, Srikakulam District, Andhra Pradesh, India, 1993–94*

	Pearson product moment correlation†		Spearman rank correlation‡	
Nutritional variable	Pre	Post	Pre	Post
Total energy (kcal day^{-1})	0.55	0.55	0.64	0.50
Total fat (g day^{-1})	0.68	0.67	0.65	0.56
Fat (% energy)	0.81	0.81	0.72	0.70
Fibre (g day^{-1})	0.70	0.62	0.71	0.53
Iron (mg day^{-1})	0.44	0.38	0.53	0.33
Sodium (mg day^{-1})	0.29	0.14	0.34	0.31
Copper (mg day^{-1})	0.62	0.48	0.61	0.36
Zinc (mg day^{-1})	0.62	0.69	0.69	0.65
Calcium (mg day^{-1})	0.56	0.32	0.65	0.37
Ascorbic acid (mg day^{-1})	0.08	0.30	−0.005	0.31
β-Carotene (μg day^{-1})	0.10	0.15	0.18	0.26
Thiamine (mg day^{-1})	0.61	0.57	0.65	0.43
Riboflavin (mg day^{-1})	0.55	0.51	0.60	0.45

* In all instances $P < 0.05$ if $|r| > 0.25$, total $n = 60$.
† This is the parametric coefficient obtained in correlating the FFQ-derived nutrient score with the equivalent 24HR-derived nutrient score.
‡ This is based on the rank order (non-parametric) correlation.

Table 2 Descriptive statistics – Diet and Oral Precancer Study, Srikakulam District, Andhra Pradesh, India, 1993–95*

	Cases		Controls	
Categorical variable*	*n*	(%)	*n*	(%)
Males	104	(21.4)	108	(22.2)
Females	381	(78.6)	379	(77.8)
Occupation				
Business/Professionals	3	(0.6)	2	(0.4)
Farming/Merchandise	25	(5.2)	39	(8.0)
Skilled labour	32	(6.6)	17	(3.5)
Secretarial/Clerical	9	(1.9)	8	(1.6)
Unskilled/Self-employed	229	(47.2)	257	(52.8)
Householder	187	(38.6)	164	(33.7)
Education				
Illiterate	451	(93.0)	451	(92.6)
Primary	21	(4.3)	24	(4.9)
Middle	12	(2.5)	6	(1.2)
High school	1	(0.2)	3	(0.6)
College	0	–	3	(0.6)
Social category				
Forward	206	(42.5)	222	(45.6)
Backward	196	(40.4)	171	(35.1)
Schedule	83	(17.1)	94	(19.3)
Socio-economic status				
Low	442	(91.1)	457	(93.8)
Medium	43	(8.9)	30	(6.2)
Tobacco use				
Chewing	3	(0.6)	18	(3.7)
Smoking	56	(11.5)	72	(14.8)
Smoking and chewing	29	(6.0)	39	(8.0)
Reverse smoking	397	(81.9)	358	(73.5)
Continuous variable†	Mean	(SD)	Mean	(SD)
Age (years)	52.1	(10.4)	51.3	(10.4)
Nutrients†‡				
Total energy (kcal day^{-1})§	1981	(408)	1998	(404)
Total fat (g day^{-1})	33.4	(22.4)	33.4	(14.2)
Fat (% energy)	15.4	(9.8)	15.2	(6.0)
Fibre (g day^{-1})	12.3	(5.0)	13.3	(5.9)
Iron (mg day^{-1})	23.3	(8.2)	24.5	(8.8)
Sodium (mg day^{-1})	83.2	(62.1)	88.7	(51.5)
Copper (mg day^{-1})	2.05	(0.70)	2.15	(0.82)
Zinc (mg day^{-1})	18.3	(5.5)	18.9	(6.1)
Calcium (mg day^{-1})	939	(452)	1046	(495.4)
Ascorbic acid (mg day^{-1})¶	4.3	(0.4)	4.3	(0.4)
β-Carotene (μg day^{-1})¶	7.4	(0.6)	7.5	(0.5)
Thiamine (mg day^{-1})	1.51	(0.56)	1.62	(0.64)
Riboflavin (mg day^{-1})	1.33	(0.38)	1.38	(0.40)

* Values presented are the number and percentages of all cases and controls with the attribute.
† Value is the mean and standard deviation (SD) by case and control status.
‡ Nutrients are daily amounts as calculated from the food-frequency questionnaire, as described in the text.
§ Energy intake is adjusted to account for overreporting of rice intake, as reported in the text.
¶ Values of these nutrients are log-transformed to normalise the distribution.

Table 3 Distribution of lesion types – Diet and Oral Precancer Study, Srikakulam District, Andhra Pradesh, India, 1993–95*

	Male		Female	
	n	(%)	*n*	(%)
Palatal changes (patches)	54	(51.9)	332	(87.1)
Palatal changes (red areas)	5	(4.8)	43	(11.3)
Leukoplakia	46	(44.2)	14	(3.7)
Submucous fibrosis	2	(1.9)	–	–
Carcinoma	–	–	2	(0.5)
Total number of subjects with qualifying lesions	104		381	

*Tabulated values are the number of subjects (cases) with each lesion. The value in parentheses is the proportion of males or females having the lesion. Because of multiple lesions, the total will add to a number greater than 100%.

contributor to intake of most of these nutrients). Exceptions were ascorbic acid and β-carotene, to which the contribution of rice is nil. It must be emphasised that the miscalibration in reporting rice intake appeared to be uniform across the whole study and it affected the intake values only through change of origin and scale. Correlation, however, is not affected by any change in origin or scale, and for most nutrients the correlation coefficients were relatively high, as they were for total energy (Table 1).

The distribution of lesions among the 485 cases is presented in Table 3. Among women, almost all lesions were located on the palate; whereas among men, slightly over half of all lesions were located on the palate. Smoking, in any form, was associated with elevated risk. Odds ratios (ORs) for smoking were consistent, irrespective of what control variables were fit in the model. In the model with no dietary or economic variables included, relative to chewing only, the OR for reverse *chutta* was 5.19 (95% confidence interval (CI)=1.35, 19.9) and for conventional smoking it was 3.63 (95% CI = 0.96, 13.74). As with results based on analyses of other data from these same study areas, alcohol intake was minimally associated with the presence of these lesions[42]. Inclusion of any other predictor, including alcohol, did not materially affect the size or significance of these relationships. When restricting the analysis to females, information on tobacco habit was omitted from the model because virtually all (98%) women tobacco users were reverse *chutta* smokers.

Table 4 presents the OR and 95% CI for each of the eight nutrients found to be related to oral precancerous lesions. Six were found to have linear protective effects and two were found to be associated with reduced risk at any level above the lowest quartile of intake. For those linearly related, we show the effect of the nutrient across the interquartile range of its distribution as a way of standardising their effects. In all models, virtually identical results were observed for all control variables. For all six nutrients fit as continuous variables, the model had higher overall explanatory ability than did the quartile alternative.

Models not shown analogous to those in Table 4 but fit for women separately showed very similar results, owing to the preponderance of women in this study. Among men, except for zinc (OR = 0.87, or a 13% reduction in risk per gram of zinc consumed per day, $P = 0.06$), the results did not approach statistical significance. However, the point estimates of the ORs were similar for men and women.

Table 4 Adjusted odds ratios for nutrients in relation to overall lesions – Diet and Oral Precancer Study, Srikakulam District, Andhra Pradesh, India, 1993–95*

	OR (95% CI)	*P*-value	Effect across interquartile range (%)†
Nutrients best fit as a continuous variable‡			
Iron (10 mg day^{-1})	0.82 (0.68, 0.99)	0.04	(16.6)
Zinc (mg day^{-1})	0.91 (0.85, 0.98)	0.02	(70.2)
Copper (mg day^{-1})	0.83 (0.67, 1.03)	0.09	(16.0)
Calcium (100 mg day^{-1})	0.95 (0.92, 0.98)	0.001	(33.6)
Riboflavin (mg day^{-1})	0.51 (0.28, 0.93)	0.03	(22.1)
Fibre (g day^{-1})	0.96 (0.94, 0.99)	0.007	(29.6)
Nutrients exerting non-linear effects§			
β-Carotene (highest 3 quartiles)	0.78 (0.58, 1.05)	>0.10	
Ascorbic acid (highest 3 quartiles, females only)	0.82 (0.59, 1.13)	>0.10	

*Nutrients shown are ones hypothesised to be related to risk of oral cancer or precancer. Odds ratios (ORs) and their 95% confidence intervals (CIs) are based on seven separate logistic regression models, one for each of the seven nutrients shown (excluding ascorbic acid). Each model controlled for type of tobacco habit and total energy consumption (kcal day^{-1}). For ascorbic acid, type of tobacco habit was omitted because virtually all women were reverse *chutta* smokers.

† For each nutrient fit as a continuous variable, the effect was standardised by computing the difference of effect at the 75th percentile value (OR×nutrient$_{75}$) and its effect at the 25th percentile value (OR×nutrient$_{25}$). The value shown represents the percentage reduction across the interquartile range. The respective 25th, 50th and 75th percentile values for each nutrient shown are as follows: iron (mg day^{-1}) – 18.5, 23.1 and 27.7; zinc (mg day^{-1}) – 14.7, 19.4 and 22.5; copper (mg day^{-1}) – 1.55, 2.04 and 2.49; calcium (mg day^{-1}) – 583, 974 and 1255; riboflavin (mg day^{-1}) – 1.11, 1.36 and 1.56; fibre (g day^{-1}) – 8.5, 12.1 and 15.9; β-carotene (μg day^{-1}) – 1180, 1675 and 2405; ascorbic acid (mg day^{-1}) – 57.2, 74.4 and 93.7.

‡ Each nutritional variable is fit as a continuous variable. The units are modified to permit easier interpretation of the odds ratio (e.g. the OR shown for calcium represents the fraction of risk with each 100 mg consumed per day).

§ These variables were found to have an effect, which was clearly non-linear. In each instance the referent is the lowest quartile of reported intake.

Table 5 Adjusted odds ratios for nutrients in relation to overall newly incident lesions – Diet and Oral Precancer Study, Srikakulam District, Andhra Pradesh, India, 1993–95*

	OR (95% CI)	Sample-size-adjusted 95% CI†
Nutrients best fit as a continuous variable†		
Iron (10 mg day^{-1})	0.82 (0.39, 1.69)	(0.67, 1.00)
Zinc (mg day^{-1})	0.88 (0.63, 1.22)	(0.80, 0.96)
Copper (mg day^{-1})	0.77 (0.35, 1.73)	(0.61, 0.97)
Calcium (100 mg day^{-1})	0.98 (0.87, 1.10)	(0.95, 1.01)
Riboflavin (mg day^{-1})	0.39 (0.03, 4.53)	(0.20, 0.77)
Fibre (g day^{-1})	0.97 (0.88, 1.06)	(0.94, 1.00)

* Nutrients shown are ones hypothesised to be related to risk of oral cancer or precancer. Odds ratios (ORs) and their 95% confidence interval (CIs) are based on six separate logistic regression models, one for each of the nutrients shown. Each model controlled for type of tobacco habit and total energy consumption (kcal day^{-1}).
† This is the 95% confidence interval adjusted for the sample size observed in the main study (based on 485 eligible lesions).

Analyses based on palatal changes consisting of patches were similar to those based on overall lesions, with significant protective effects for calcium (OR = 0.95; 95% CI = 0.92, 0.98), riboflavin (OR = 0.46; 95% CI = 0.23, 0.93) and fibre (OR = 0.97; 95% CI = 0.94, 0.99). Point estimates of the OR in women and in men were virtually identical (though none were statistically significant in men). Results from analyses of palatal changes consisting of red areas showed a protective effect of zinc in the higher quartiles of intake: for quartile 2, OR = 0.11 (95% CI = 0.02, 0.57); for quartile 3, OR = 0.09 (95% CI = 0.01, 0.74); and for quartile 4, OR = 0.05 (95% CI = 0.003, 0.80). Results in women were identical to the overall results. There also was a larger decrease in risk from calcium (OR = 0.92, 95% CI = 0.82, 0.99) for red areas, as compared with patches. Leukoplakia-specific results were unremarkable, with only suggestions of protective effects in women for zinc (OR = 0.38; 95% CI = 0.14, 1.08), fibre (OR = 0.80; 95% CI = 0.61, 1.05) and calcium (OR = 0.73; 95% CI = 0.52, 1.02).

Analyses focusing on newly incident cases (Table 5) were meant to corroborate the results of the main case–control study shown in Table 4. Due to the small sample size and the confirmatory nature of that portion of the study, there was neither an intention of formal hypothesis testing nor one of examining effects in any subset of the data. Among individuals who were originally lesion-free, 39 were found to have one or more lesions after one year (cases). One such person was included as a control in the main case–control study, but was classified as a case in this follow-up dataset. All female cases were reverse *chutta* smokers. Of the 32 women with lesions, 30 had palatal patches and two had red areas. Among seven new male incident cases, five were diagnosed with leukoplakia, one had palatal changes, and one had lichenplanus. Despite very wide confidence limits, as expected, the point estimates of the ORs were similar to those presented in Table 4. When we 'adjusted' the 95% CI to the size of sample in the main study, they were very similar to those shown in Table 4.

Discussion

Studies attempting to relate diet with oral cancer must confront two major obstacles, one inherent in the relationships among relevant risk factors and the other a consequence of the distribution of oral cancer in human populations. In most populations, oral cancer is strongly related to either tobacco use or alcohol consumption or both[11]. Typically, these two risk factors are related to diet, with tobacco users consuming diets that are otherwise less healthy than diets of non-tobacco users[43,44]. As such, these risk behaviours have the potential to confound the apparent effect of dietary factors. Besides relationships among risk behaviours, there are organic relationships among dietary constituents and those related to the use of tobacco. For example, products of tobacco combustion will create a demand for antioxidants, such as β-carotene, whose only source (at least in a population such as this) is dietary. Thus, smoking is an important determinant of serum β-carotene levels, even in subjects who are apparently healthy[45,46]. This demand might be increased in subjects with cancers or precancerous conditions, especially in those who continue to smoke. So, while the use of biomarkers of dietary exposure may have conceptual appeal, tissue levels may not be an adequate reflection of dietary intake (although it may have relevance to tissue-level exposure to the nutrient or its metabolite). In studies using serum levels of β-carotene as a biomarker[47], unless smoking is carefully measured and controlled in analyses, some of the variability in β-carotene levels will be explained by tobacco smoking, and inferences regarding dietary β-carotene almost certainly will be confounded, even in cohort studies of subjects who are apparently healthy when recruited[45,46].

The second obstacle in the design and execution of epidemiological studies is the fact that oral cancer is a rare disease in most populations. Therefore, it has been amenable to study mainly using case–control designs. Such designs are subject to biases in self-report, arising either directly or indirectly from changes in exposure to risk factors, especially diet, concomitant with the onset of disease symptoms[11,19] or to beliefs held by research subjects regarding the causes of disease or disease progression[48]. Because oral cancer is likely to affect the diets of oral cancer patients and diet–cancer hypotheses have been popularised in many populations, such studies are limited by the potential for biased dietary recall among the cases as compared with the controls[11]. Apparently, there is no specific scientific literature on beliefs or attitudes about diet in relation to cancer in India, although there are widely held beliefs about diet and health more generally[49].

In this study, we were careful to enrol only users of

tobacco and then to measure their exposure to tobacco products very carefully using methods that had been developed and refined through years of study in this population[12,50]. In designing this study, a decision was made to focus on precancerous lesions. This was done to increase outcome yield and to reduce the probability of biased dietary exposure estimates due to the presence of a condition that could affect the physical sensation and palatability of food among the cases. Our prior research had indicated a high relative risk of the precancerous lesions seen in this population progressing to frank cancer[14]. By studying these conditions earlier on in the natural history of the disease, there would be a better chance of measuring diet during the more aetiologically relevant period. Finally, in order to reduce further the probability of bias, we chose to withhold the diagnosis of the condition from both the subject and the interviewer until the diet interview was completed (<5 days from the exam).

Oral precancerous lesions included in this study, with the exception of oral submucous fibrosis, produced no symptom that would materially affect the usual diet of the affected individual. Oral submucous fibrosis almost invariably causes a burning sensation on intake of spicy food and since the food in this part of India is especially spicy, that could cause some changes in usual diet. Following the study protocol, oral submucous fibrosis cases were included in the case group even though there were only two and they would not have materially affected findings. It was not feasible to conduct a separate analysis for oral submucous fibrosis, as was done for the Gujarat study[10].

Study findings in context

As expected, the strongest relationship observed was that between reverse *chutta* and palatal lesions, which represented the most common tobacco habit and most common lesion type, respectively. As with other studies in India, there was no affect of reported alcohol exposure[42]. This may be due to the dominance of tobacco use in causing these lesions or to relatively low rates of exposure to alcohol.

Judging by the size of the effect across the interquartile range of exposure (Table 4), the strongest dietary relationships observed in this study were the protective effects of zinc, calcium and fibre. The observed effect of zinc is consistent with that reported in another study in reverse *chutta* smokers[22,25]. Zinc is a necessary component of over 200 enzyme systems necessary for the proper differentiation and growth of cells and as a structural constituent of many proteins, hormones, neuropeptides, hormone receptors and probably polynucleotides[51]. Like zinc, iron showed a linear (though weaker) effect in these data. Also like zinc, iron may be important for proper differentiation of epithelial tissue and other potential mechanisms of carcinogenesis[52–55].

In a hospital-based case–control study in China, it was found that dietary fibre derived from fruits and vegetables showed a strong negative association with oral cancer risk[47]. These results were similar to those from a population-based case–control study in which risks decreased with increasing intake of fruits and some vegetables[27]. In another case–control study in the USA, it was observed that dietary fibre was associated with decreased risk[29]. Calcium, however, had not been observed to have a strong relationship with oral cancer previously. There is some suggestion that Ca^{2+} release affects cell rounding and retraction in human oral cavity epidermoid carcinoma cells[56]. There is one case–control study that reports higher nail concentrations of iron and calcium in oesophageal cancer cases than in controls[57]. Still, these findings pertain to a different site and histological type and, in frank cases of cancer, there may be metabolic alterations that further obfuscate the relationship between diet and disease.

Results of a survey of a population with a high risk of oral and oesophageal cancer (in Uzbekistan) indicated that blood levels of retinal, carotene and riboflavin were lower among individuals with these conditions[28,58]. The use of blood measures in people with frank disease may lead to biased estimates of exposure relative to typical diet in the aetiological period of interest, irrespective of the effect of smoking on tissue levels of antioxidants. Analysing data collected before disease onset, a nested case–control study in Washington County, MD showed that serum levels of carotenoids and α-tocopherol were lower among subjects who developed oral and pharyngeal cancer than in matched controls who were free of disease[59]. Because of its design, that study was able to circumvent problems with disease-related biases[59].

Sodium, ascorbic acid and β-carotene showed some of the lowest correlation and regression coefficients in comparing the FFQ- and 24HR-derived dietary data. Also, these three nutrients were only weakly associated with the lesions, if at all. It may be that these two observations are related; i.e. to some extent imprecision in estimating intake may explain the lack of strong relationship with disease status. In our data, there was a suggestion that β-carotene intake in the highest quartile (here estimated to be $>2.4\,mg\,day^{-1}$) may be protective. That this is still far below pharmacological range is consistent with findings from other studies on the effect of β-carotene in the physiological range[23,60–63].

In this study, riboflavin was found to be protective. In one case–control study conducted in Western New York State, riboflavin was associated with increased risk[29]. However, in another case–control study from Italy, an increased maize intake among cases with cancers of the oral cavity, pharynx and oesophagus was reported[30]. Because maize can cause deficiencies of riboflavin, this result is consistent with a broad range of evidence indicating a protective effect of this B vitamin from

studies conducted in Africa, China, the United States and Italy[30].

In an intervention trial of reverse *chutta* smokers from Srikakulam District, using the frequency of micronucleated cells and DNA adducts as indicators of DNA damage, it was reported that supplementation with four nutrients (vitamin A, riboflavin, zinc and selenium) reduced micronuclei and DNA adducts in subjects both with and without precancerous lesions at the beginning of the study[25]. It also was found that these same nutrients were related to a reduced incidence of oral precancerous lesions[22]. In a randomised, double-blind intervention trial conducted in a population with a high incidence of disease in Huixian, People's Republic of China, there was only a weak suggestion of protective effects of riboflavin and zinc[64].

The incident oral precancerous lesions diagnosed during follow-up after one year (39 cases) and an equal number of matched controls examined and interviewed exactly in the same manner as in the case–control study provided a built-in check for the results obtained in the main case–control study. Although the one-year dataset afforded little statistical power, it did provide a unique opportunity to compare point estimates of the OR with those from the main case–control study. When we adjusted the 95% CI for the sample size in the main case–control study we found that they were remarkably similar, indicating that the wide confidence limits were due to small sample size and not heterogeneity of effect. In the main case–control study, no estimate of the duration of the presence of the lesion was possible and there could have been some undetermined heterogeneity with regard to that in the case group. Analysis of these 39 incident cases addressed that problem and it was reassuring that the results were very similar.

Weaknesses and recommendations for future study

Because of the uniformly low level of education in this population, it was not possible to control for it in analyses or to examine covariance in other factors (e.g. dietary calcium) with which it may be related. Future work in this population should aim to enrol subjects with a wider range of educational attainment.

Except for two studies on which we reported from Gujarat[10] and Kerala[9], studies of diet and cancer previously reported from India have used simple diet checklists and FFQs inadequate for the purposes of nutrient estimation. In Andhra Pradesh, a large portion of the adult population is illiterate. This fact, as well as our need to standardise collection methods to the extent possible, compelled us to use the interviewer-administered FFQ. Testing of this instrument was conducted in an external validation study in a population similar to that used as the basis of the case–control study. Results indicated a relatively high level of agreement between nutrient consumption data derived from this FFQ and data derived from eight days of 24HR administered over a one-year period. This was true even for total caloric intake to which rice was a major contributor and occurred despite an obvious miscalibration in reporting intake of rice preparations. The overestimate in rice intake was similar in direction to the social approval bias that we have observed among men in the USA[48,65], but of somewhat larger magnitude. Unlike results in both Gujarat[34] and Kerala[33], the overestimate affected both the 24HR-derived and the FFQ-derived estimates. Given the high level of importance attached to food in India, future work should focus on understanding the source of the bias and methods developed to minimise its effect.

Rather than make *post hoc* adjustments to account for miscalibration, we used the actual values in all analyses. As with most epidemiological studies of diet and cancer in humans, this study produced ORs as estimates of relative risk of exposure to these nutrients and this miscalibration would not affect these estimates. By not adjusting, we have avoided adding possible error to the estimated relative risk. Still, estimating exact nutrient dose–response relationships would be problematic because of the overreporting of rice intake (i.e. real exposure levels would be lower than percentile scores shown in Table 4).

Summary

The results of this study, unencumbered by the kind of biases that normally would beset a study of nutrition and oral cancer, indicate a protective effect of several micronutrients in oral precancerous lesions in a population exposed to tobacco. In its design, we recognised the potential for intractable confounding and took advance remedial steps such as the use of blinded interviews to minimise the possibility of bias associated with diagnosis, referral and assessment procedures. A focus on oral precancerous lesions offered a particularly good opportunity for research since, unlike oral cancer, the individual was generally not aware of the lesion and had few, if any, associated symptoms that might affect dietary intake. Results from this study support consumption of a nutrient-dense, vegetable-based diet in reducing risk of oral precancerous lesions, a conclusion consistent with that reached by a variety of governmental and non-governmental agencies[66–68]. Even though a disease-related bias was unlikely, future work should focus on identifying and controlling for more generalised (i.e. non disease-related) biases in the self-reporting of dietary intake.

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Appendix D

THE SCHOOL PHYSICAL ACTIVITY AND NUTRITION (SPAN) SURVEY, PHASE II: EVALUATING OVERWEIGHT AND OBESITY IN TEXAS SCHOOLCHILDREN

ABSTRACT

The prevalence of overweight and obesity among children has almost doubled in the last twenty years, and rates are highest among minority populations. With the link between obesity and the development of chronic diseases such as cardiovascular disease and type 2 diabetes, obesity in youth is a significant public health concern. Before specific interventions can be developed to target obesity in schoolchildren, it is necessary to first identify the prevalence of obesity at both the state and regional level. *Until a surveillance system is established in Texas, evaluation of any state- or region-wide interventions or policy efforts cannot be adequately ascertained.*

The overall goal of this project is to develop a surveillance system to monitor secular trends in body mass index (BMI) of school-age children in the 4th, 8th and 11th grades within ethnic and geographic subpopulations. In addition, information about the mediating factors that underlie obesity (dietary and physical activity behaviors, nutrition knowledge and attitudes) will be collected. The sampling scheme for this project involves a two-phase approach in which half of the TDH regions are assessed each year to obtain a sample that is representative at both the state and regional level. During Phase I of the proposal (2000-2001), data were obtained from 5 Texas public health regions (1,3,5,7, & 11). For Phase II, the materials and experiences from Year 1 will be used to measure students from the remaining 6 public health regions (2, 4, 6, 8, 9, & 10). As proposed, the sampling scheme will provide a state-representative sample each year, and regional specific samples every other year. Fifteen schools at each grade level (elementary, middle and high school) are sampled from each region: 5 from the largest urban district in the region, 5 from other urban/suburban districts and 5 from rural districts. Two classes of students from 4th, 8th and 11th grades are sampled from each school, for a total of 30 classes per grade level per region.

The surveillance system utilizes instruments and protocols developed as part of the School-Based Nutrition Monitoring (SBNM) project and SPAN, Phase I, including a school-based protocol for height and weight measurements, and a student questionnaire. The student questionnaire was designed to assess food choice behaviors, food selection skills, weight perceptions and practices, nutrition knowledge, attitudes about food and eating, and physical activity behaviors, all of which are factors contributing to childhood obesity. Students complete the questionnaire in class; height and weight measurements are recorded on the questionnaire to link the biological and behavioral data.

Coordination of data collection is through partnership with TDH, and involves TDH regional nutritionists, wellness staff, and Texas Agricultural country extension agents as data coordinators. Project staff implement a "train-the-trainer" model, in which state data coordinators are trained by the investigative staff; these state data coordinators will then train the school nurses or teachers to conduct height and weight measurements and/or administer the survey instruments at the local level. Quality control procedures are implemented at each stage of data collection, to ensure reliability and validity of the measurements. Data are analyzed, and results presented as state and regional level data.

Information from this surveillance system will assist state and local entities in developing targeted programs and policies to address overweight and obesity among youth in Texas.

Appendix E

Pre-Proposal Title Page

1. Proposal Title: Interrelationships of Hormones, Diet, Body Size and Breast Cancer among Hispanic Women
2. Award Category: HBCU/MI Partnership
3. PI's Full Name: Gerson Peltz
4. PI's Phone Number: (956) 554-5063
   PI's Fax Number: (956) 554-5043
   PI's E-mail Address: gpeltz@utb.edu
5. Organization Name and Location: University of Texas at Brownsville, Brownsville, TX, 78520, USA
8. Key Words: Estrogen, body size, insulin resistance

Pre-Proposal Body

1. Background

1.1 Overview of Breast Cancer in the Lower Rio Grande Valley

The Lower Rio Grande Valley (LRGV) is comprised of the four counties at the southern tip of Texas on the Mexico border. The population of the LRGV is 85 percent Hispanic, and its major cities are Brownsville, Harlingen and McAllen. The Texas Cancer Registry reported breast cancer incidence rates for 1995-1997 of 100.1/100,000 for the state and 89.1/100,000 for Public Health Region (PHR) 11, which encompasses the LRGV. In PHR11, these rates are highest among non-Hispanic Whites (121.2/100,000), followed by African Americans (93.0/100,000) and by Hispanics (73.6/100,000). From 1990-1999, breast cancer was the second leading cause of cancer deaths among women in Texas (23.1/100,000) and PHR 11 (19.5/100,000). Breast cancer mortality of Hispanics in PHR 11 has increased over time, evidenced by the 1990-1999 rate (17.3/100,000) that is approaching the non-Hispanic white rate (23.1/100,000). It is important to note that breast cancer incidence rates in this region may be underestimates because cancer is severely underreported and many persons seek medical care across the border in Matamoros, Mexico. A long-term goal of this partnership would be the development of a regional cancer registry for the LRGV.

1.2 Minority Institution - University of Texas at Brownsville/Texas Southmost College

In 1991, the Texas Legislature passed legislation that created the University of Texas at Brownsville (UTB) and Texas Southmost College (TSC). The partnership combined a junior college, the first institution of higher education in the Lower Rio Grande Valley created in 1926, with a free-standing upper-level university. As "America's first Community University," the mission of the UTB/TSC partnership is to provide accessible, affordable, post-secondary education of high quality, to conduct research, which expands knowledge, and to present programs of continuing education, public service, and cultural value to meet the needs of the community. In November 1996, UT System Board of Regents approved the university's application for single accreditation and in May 1997 both boards signed the agreement. The first five years of the partnership were dynamic. The partnership used its combined resources to continue creating new degree programs, serve a growing student population and to expand campus infrastructure to serve the local community. Located at the southernmost tip of the State of Texas, UTB/TSC currently occupies some 350 acres adjacent to the US/Mexico border near Tamaulipas, Mexico. UTB/TSC is the only public university in Texas that offers certificate through master degree level with cooperative agreements offering options for doctoral programs. A snapshot of the student profile reflects a student enrollment of approximately 9,500, 92.3 % Hispanic, average age of 25.6, with over 80% requiring some form of financial assistance.

Heretofore, university faculty have been involved in modest research endeavors, however in the last five years have initiated scientific research activity through the biology, behavioral sciences and engineering programs, particularly, and have actively recruited faculty that contribute significantly to scientific research and investigation. Current research and study is being conducted in the areas of neuroscience, nutrition and genetics. UTB/TSC is committed to encouraging research among its biological and health sciences faculty and recognizes that release time is an essential component of that design. The institution requires that the faculty be engaged continually in its own development or improvement, and believes that growth is mandatory for faculty, as well as students. It recognizes its responsibility not only to require that the faculty advance professionally, but to facilitate such advancement. The university's

objective is to promote and facilitate faculty development in teaching, research or scholarship, and participation in professional organizations. The President and Provost/Vice President of Academic Affairs have concurred that a program and policy of "release time" be developed as part of this program. It is also intended that trained faculty then work with other colleagues to encourage and mentor future researchers at the university. Faculty will be allowed time to participate in training seminars, conferences and educational events relevant to the continued development of research at the university.

1.3 Collaborating Institution - University of Texas Health Science Center Houston School of Public Health

In 1998, State legislation was passed that created the Lower Rio Grande Valley Regional Academic Health Center consisting of a medical school in Harlingen, basic science school in Edinburg, and public health school in Brownsville. This creation was a boon to the Lower Rio Grande Valley, contributing greatly toward providing educational opportunities for medical school students, community education and public health education and research. In 1999, the University of Texas Health Science Center Houston School of Public Health (UTSPH) offered its first classes on the UTB/TSC campus in Brownsville. The only UTSPH degree offered in Brownsville is the Master of Public Health with options in Behavioral Sciences, Biological Sciences, Biometry, Environmental and Occupational Health Sciences, Epidemiology, and Management and Policy Sciences. The Brownsville regional campus works cooperatively with the UTB/TSC Master of Science in Public Health Nursing program by providing classes in the core areas of public health. The UTSPH Brownsville recently moved into new facilities in 2002, which includes two interactive television (ITV) classrooms with state-of-the-art equipment enabling students in Brownsville to participate in classes offered by faculty in Houston and other regional campuses. About 3000 square feet of laboratory space is also available which will accommodate environmental health, genetic and serological studies as needed. There will be facilities for tissue culture, viral and bacteriological cultures, polymerase chain reaction and serology.

The location of the new UTSPH Brownsville on the UTB/TSC campus offers enormous possibilities for partnerships and collaborations in research, health promotion and public health. The vision of the Brownsville regional campus of the UTSPH is to conduct community-based participatory research in areas deemed important by the community. The proposed project fits nicely with the UTB/TSC community's commitment to expanding scientific research and investigation. In addition, UTSPH Houston has an established history in medicine, biomedical and medical research, public health research and investigation.

2. Collaborative Arrangement

2.1 Overview of Collaborative Arrangement

The HBCU/MI Partnership Training program will provide the opportunity for UTB/TSC faculty to benefit from the wealth of information available through consultation, mentoring and training with scientists and researchers from the UTSPH, at the Brownsville regional campus and at the main campus in Houston. Initial meetings with the faculty have proven extremely productive and both faculties have identified mutual interests that are worthy of future exploration and scientific investigation relevant to breast cancer research.

2.2 Minority Institution - University of Texas at Brownsville/Texas Southmost College

Dr. Gerson Peltz, principal investigator from the minority institution has conducted preliminary studies on the interrelationships of hormones, body size and breast cancer. Dr. Peltz

is a Professor of Biological Sciences at UTB/TSC and has recently submitted a proposal to investigate the role phytoestrogens play in breast cancer risk among Hispanic women.

Epidemiological studies have provided strong evidence that dietary patterns play an important role in the etiology of some of the most common cancers (1-3). The relation between nutrition and cancer is probably much more complex and involves various lifestyle factors in addition to single dietary composition. Ovarian hormones strongly contribute to breast cancer etiology. Elevated serum estrogen levels and increased urinary excretion rates of estrone (E_1), 17β-estradiol (E_2), and estriol (E_3) have been found in breast cancer cases as compared with controls (2). Phytoestrogens, a group of biologically active compounds found in soy-based and plant-based foods, have been shown to reduce the level of endogenous estrogen in the body, which may have an effect on the onset of breast cancer. Phytoestrogens have the property to influence intracellular enzymes, protein synthesis, growth factors, malignant cell proliferation, and angiogenesis (4). Finally, the body fat content also plays an important role in the genesis of breast cancer. Body fat content is related to body estrogen storage and release.

Studies have shown that phytoestrogens play a role in the reduction of breast cancer risk (5). Phytoestrogens are classified into two main categories: isoflavones and lignanes. The two main isoflavones are genistein and daidzen, which are found in leguminous vegetables and soybeans. Lignanes are found in high concentration in linseed and fiber-rich foods. The two main lignanes are enterolactone and enterodiol. Many factors influence the availability of isoflavones and lignanes after ingestion, especially the presence of fibers and the individual characteristics of metabolism (6). There is a geographical variation of breast cancer risk. It is higher in the United States and Western Europe, and lower in Chinese, Japanese, Asian women in general, and the Hispanic population. One possible explanation for the differences in breast cancer risk is the consumption of phytoestrogens and their relationship with the estrogen circulating levels. Phytoestrogens can be considered weak estrogens presenting an activity 100 to 1,000 times lower than 17β-estradiol (E2). The similar chemical structure of phytostrogens and estrogens allow both to bind to estrogens receptors (ER). ERα is a receptor associated with increased cell proliferation and breast cancer risk Genistein and daidzen have a lower affinity for ERα than estradiol suggesting a protective effect of these compounds (5, 6).

Other potential collaborators from UTB/TSC include Dr. Nancy McGowan whose interest is behavioral sciences, and Anne Rentfro whose interest is access to care.

2.3 Collaborating Institution - University of Texas Health Science Center Houston School of Public Health

Dr. Maureen Sanderson, the principal investigator from the collaborating institution has a Department of Defense Career Development Award to investigate interrelationships of prenatal and postnatal growth, hormones, diet and breast cancer. Dr. Sanderson is an Associate Professor of Epidemiology at the Brownsville regional campus of the UTSPH, and has recently submitted a proposal to investigate the association between insulin resistance and breast cancer.

Endogenous estrogen, specifically estradiol, has been implicated as a causal factor for breast cancer (7). Critical periods of estrogen exposure are thought to be *in utero*, following menarche and around perimenopause (7, 8). Factors associated with intrauterine estrogen exposure and prenatal growth, such as birth weight, have been related to breast cancer (9). Breast cancer associated with measures of postnatal growth, such as adolescent and adult weight and height, appears to differ by menopausal status (10). The different effect of weight and height on breast cancer by menopausal status may be explained, in part, by hormonal changes. Lower adult estrogen levels have been associated with low-fat, high-fiber diets (11). Insulin-like

growth factor 1 (IGF1), which has been linked to breast cancer in several studies, may act in combination with estrogen (12). IGF1 concentrations are positively associated with height and body mass (13). Adults who were born at relatively low weights and who then become obese may have increased IGF1 and insulin levels (14). Decreased IGF1 concentrations have been associated with a low-calorie diet (15). Retinoids and vitamin D analogues also may lower IGF1 levels (16). Insulin resistance, like type 2 diabetes, is a condition characterized by high levels of insulin and by abdominal obesity (17). Excess weight gain and a high-fat, low-fiber diet may result in insulin resistance (18). Insulin resistance may place a woman at greater risk of developing breast cancer (19). The risk of breast cancer among Hispanic women may be related to their higher genetic susceptibility to insulin resistance.

Other potential collaborators from UTSPH Brownsville include Dr. Sue Fisher-Hoch with expertise in biological sciences, Dr. Adriana Perez with expertise in biostatistics, and Dr. Shelton Brown with expertise in health economics. Potential collaborators from UTSPH Houston include Dr. Guillermo Tortolero-Luna with expertise in cancer biology, Dr. R. Sue McPherson with expertise in nutrition and cancer, and Drs. Sally Vernon and Maria Fernandez with expertise in cancer screening and behavioral sciences.

3. Training Program

3.1 Overview of Training Program

This proposal is envisioned as occurring in two phases the Training Phase and the Investigation Phase. Three UTB/TSC faculty investigators will participate in the training program initially. UTB/TSC faculty will undergo intensive training provided by UTSPH faculty during years 1 and 2. To reinforce training, faculty from UTB/TSC and UTSPH will conduct a population-based case-control study of breast cancer to investigate its' association with hormones, diet and body size in years 3 and 4. An overall goal is to provide opportunities for UTB/TSC faculty to participate in research and mentor other UTB/TSC faculty with similar interests. UTB/TSC and UTSPH investigators will work together to build infrastructure to conduct case-control studies of breast cancer, to maintain local data relevant to breast cancer, and to initiate studies to investigate factors which may affect this population.

3.2 Training Phase

Specific activities to be completed in year 1 include: 1) UTB/TSC faculty will attend classes, presentations and seminars to gain knowledge of cancer biology, behavioral sciences, biostatistics, health economics, and nutrition, molecular and genetic epidemiology offered by UTSPH faculty in-person from Brownsville and via ITV from Houston, 2) UTB/TSC faculty will work with UTSPH faculty conducting analyses of preexisting breast cancer studies to become familiar with data collection and scientific field based methods, 3) the project team will liaise with local medical providers, health clinics and state health agencies to encourage reporting of breast cancer to the Texas Cancer Registry, and 4) the project team will identify sites for data collection with local health providers and health clinics.

Specific activities to be completed in year 2 include: 1) UTB/TSC faculty will continue to attend training programs offered by faculty from UTSPH, 2) the project team will develop a questionnaire for use with the local Hispanic population, 3) after consultation with local health providers and established breast cancer researchers the project team will design a case-control study to include completion of a questionnaire, anthropometry and a blood draw, 4) the project team will initiate institutional review board approval through local and federal channels, and 5) the project team will pilot test study methods and revise the study design as needed.

3.3 Investigation Phase

Specific activities to be completed in year 3 include: 1) the project team will contact breast cancer cases identified by local health providers to complete the questionnaire, body fat assessment and blood draw, 2) the project team will utilize random digit dialing to identify and contact controls for study participation, 3) the project team will assay blood samples for E2, IGF1, and other hormones and growth factors, 4) the project team will consult with local health providers and health clinics regarding the reporting mechanism and provide training as needed, and 5) the project team will expand data collection to cancers other than breast cancer as a means of developing a regional LRGV cancer registry.

Specific activities to be completed in year 4 include: 1) the project team will complete collection of data from cases and controls and assay of blood samples, 2) the project team will perform statistical analyses to assess the interrelationships of hormones, diet, body size and breast cancer, 3) the project team will disseminate findings to the Texas Department of Health, the Department of Defense, and local health providers and health clinics, 4) the project team will report findings and recommendations in peer-reviewed medical literature, and 5) the project team will submit proposals to conduct larger population-based case-control studies of cancers prevalent in the LRGV.

4. Communication

In addition to attending courses in-person in Brownsville and via ITV in Houston, UTB/TSC faculty will travel to the Houston campus at least twice during year 1 for seminars or related courses. The project team will meet weekly via ITV to discuss the progress of the breast cancer research and training program, and to address areas in need of improvement. The deans of the UTB/TSC School of Health Sciences and UTSPH Brownsville will meet at least monthly to discuss the HBCU/MI Partnership Training program, and administrators from UTB/TSC and UTSPH Houston will meet annually to discuss the potential for other collaborations. It is crucial that investigators have the support and input of local health providers; therefore, periodic meetings will be held with local oncologists and other medical professionals.

Preliminary meetings with faculty show that local research efforts are thwarted by the lack of reliable data or reporting mechanisms regarding cancer. The development of the reporting mechanism and infrastructure to support the gathering of relevant information regarding the local population will require a significant investment of time in the local community, networking with clinics, health centers and with private physicians. During the course of this training and investigation, community education seminars will be arranged through the UTB/TSC Medical Services Continuing Education program.

Both Universities will share facilities such as the UTPSH Brownsville laboratory, library, telecommunication and related interactive equipment to support the training and research goals of this program. The close proximity of facilities will be extremely convenient, cost-effective and beneficial for planning and community. With support from the Department of Defense, HBCU/MI Partnership Training Program, UTB/TSC will be able to develop necessary infrastructure for research in breast cancer and related areas. Considering the growth among Hispanics across the nation, the LRGV may prove to be a critical area in the investigation and reporting of significant epidemiological findings. With this combination of research expertise and the ability to support future efforts locally we anticipate remarkable results. The UTB/TSC biological and health sciences faculty are eager to pursue this collaboration with the UTSPH Brownsville.

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Appendix F

Introduction to Genetic and Molecular Epidemiology
Spring 2002

Instructors:	Xifeng Wu, MD, PhD, Debbie del Junco, PhD, and Corinne Aragaki PhD
Time:	Tuesdays and Thursdays, 5:00 – 7:00
Place:	Interactive Television Room {Dallas: V7-114 (Code: 2951)}
Credit Hours:	4
Prerequisite:	None
Recommended:	Introduction to Epidemiology Introduction to Biometry (or Biostatistics)
Office:	RAS W1022/HMB 2.208 (Wu), RAS W626 (del Junco), V8.112B Dallas (Aragaki)
Office Hours:	By appointment
Phone:	713-745-2485 (Wu), 713-500-9239 (del Junco), 214-648-1054 (Aragaki)
E-mail:	xwu@notes.mdacc.tmc.edu, ddeljunco@sph.uth.tmc.edu, Corinne.Aragaki@UTSouthwestern.edu
Text:	The required texts are Molecular Epidemiology: Principles and Practices by Paul A. Schulte and Frederica P. Perera (Academic Press, Inc., 1993) and Statistics in Human Genetics by Pak Sham (Oxford University Press 1997).
Class Notes:	To offset some xeroxing costs, please pay your local class representative $10 (Debbie in Houston, Corinne in Dallas, and Maria Elena Rodriguez in Brownsville) by the end of the month.
Website:	http://www2.utsouthwestern.edu/publichealth/Aragaki/Classes/index.htm (there's a link to the Genetic and Molecular website, just too cumbersome to type).

1. BACKGROUND AND OBJECTIVES

Companion course to Molecular Epidemiology. Molecular Epidemiology is designed as a survey course for students with a background in genetic epidemiology. If you lack that background or wish to know more about genetic epidemiology, this course will provide context for the molecular epidemiology portion of the class. In addition to an overview of molecular biology, genetics, statistics, and epidemiology, this course will presents methods and techniques for genetic and molecular epidemiology studies. Emphasis will be placed on the application of biomarkers analyses using linkage and linkage disequilibrium. Advantages and limitations of using biomarkers in epidemiologic studies will be discussed.

The objectives of this course are:

1. To enable students to critically review the scientific literature that deals with research and advances in genetic and molecular epidemiology.

2. To enable students to communicate and facilitate interdisciplinary research with geneticists, biochemists, toxicologists, microbiologists, cellular and molecular biologists and other scientists who have research expertise in the measurement of human exposures and disease susceptibility.

3. To enable students to design a valid genetic and molecular epidemiologic study that incorporates relevant biomarkers.

4. To enable students to be able to conduct simple linkage and linkage disequilibrium analyses.

2. EVALUATION:

1. **Lab Assignments** (30%)

Short lab assignments which provide an opportunity to apply the concepts and skills discussed in the lecture will be given. Lab assignments will be discussed in class, and all students will have the opportunity to lead the class discussion. Students will submit individual write-ups for grading.

2. **Class Project** (50%)

All students are expected to complete a final class project. The write-up of the project should be no longer than 15 pages (typed, double-spaced) and will be comprised of the following:

a. *Hypotheses/research question and background.* State not only the research question you intend to answer but also the reasons you are interested in exploring this particular question. Use references to back up the rationale behind your hypothesis.

b. *Study design and justification.* Given your hypothesis/specific aims, design a study and justify design choice.

c. *Sample description.* Describe the study population you are proposing to use to explore your research question. You may want to include a description of the demographic characteristics of your study sample as well as a short discussion about the limitations (if any) of your study sample, especially with respect to generalizability.

d. *Statistical methods.* Identify the statistical method of analysis you will use to answer your research question and provide justification for that choice.

e. *Discussion/comments.* Discuss your proposal with respect to (1) the limitations of your ability to answer your research question as originally proposed; (2) what you found most significant/interesting/innovative about your method. Relate this to your rationale.

You will submit small portions of your project throughout the semester to help us

monitor your progress and make sure you have chosen a manageable project. Although the small assignments will not be graded formally, failure to turn these in will hinder your progress in completing the project and will negatively affect your course participation grade. The due dates associated with the project are as follows

Project proposal - Identify your topic area, data source, and rationale. (1 page). **Due Feb. 14.**

Project outline - Identify the research question(s) you are considering for exploration, the data sources and variables, and the statistical tests and rationale you plan to use for investigating your question(s). (1 page). **Due Mar 28.**

Final project - **Due May 2.**

3. **Class participation or just demonstrated interest in the class** (20%).

4. **Bonus points** (maximum 10%). (½ per term) For each molecular/genetic epidemiology term that you define in writing such that we can include it in the class website.

Policies regarding class assignments:

1. All assignments are due at the beginning of class on the day they are due. Assignments which are received after that time will be subject to an automatic 10% point deduction unless prior arrangements have been made with the course instructor. Requests to turn in assignments at times other than the due date must be submitted to the course instructor in writing prior to the due date. The course instructor will notify the student in writing whether or not the request is approved.

2. Although students may work together on the details of some assignments (i.e., in class work on the lab assignments), students must work independently in preparing the written assignments.

- Final Exam. Short independent project that will consist of writing a design of a molecular epidemiology study. Specific format and requirements for this project will be discussed in class.

Jan. 15, 17	(Wu) Introduction to Molecular Epidemiology Molecular Biomarkers; Classification of Biomarkers (Exposure, Biomarkers, Genetic Biomarkers, Disease Biomarkers, and Intervention Biomarkers)	Course introduction - Basic genetic and molecular concepts review Available databases – gDB, Entrez, OMIM, HuGENet, linkage.rockefeller.edu, etc.
22, 24	(Fraizer) Intro to Molecular Biology (Zhu) Core techniques and applications in molecular epidemiology	**Discuss Lab Assignment #1: Internet information sources** (del Junco) Intro to genetic study design: familial studies/aggregation, twin studies
29, 31	(del Junco) Intro to epidemiology/ Design Considerations in Molecular Epidemiology	Likelihood and statistical conceptual review
Feb. 5, 7	(Amos) Statistical Methods in Molecular Epidemiology (Aragaki) Family Study, and Genetic Epidemiology	Segregation and multiple stage sampling
12, 14	(Aragaki) Gene- Environment Interaction	Study design and simple analysis for Transmission Disequilibrium Test **PROJECT PROPOSAL DUE** **Discuss Lab Assignment #2: Familial studies**
19, 21	(Bondy, Chamberlain) Biosample Banking Ethical Use of Banked Samples, Informed Consent Process for Genetic Information, Application of Risk Information to Cancer Prevention and Control, Moral, Ethical and Legal Issues	TDT and relative designs continued
26, 28	(Wu, Schabath, Zhao) Molecular Epidemiology Laboratory Tutorial **DISCUSS TAKE-HOME MIDTERM**	Introduction to Genehunter preliminaries and Genehunter with TDT
Mar. 5, 7	**SPRING BREAK**	

Mar. 12, 14	(DiGiovanni) Models of Carcinogenesis (Ananthaswamy) UV-Induced Carcinogenesis	Single point linkage analysis
19, 21	(del Junco) Metabolic Genetic Polymorphisms and Cancer Susceptibility (Wu) DNA repair Genetic Polymorphisms and Cancer Susceptibility **MIDTERM DUE**	**Discuss Lab Assignment # 3: TDT** Multipoint linkage analysis
26, 28	(El-Zein) Introduction and basis of cytogenetics (Wu) Genetic Instability and DNA Repair DISCUSS FINAL PROJECT	Nonparametric linkage analysis **PROJECT OUTLINE DUE**
Apr. 2, 4	(Bondy) Identification of Susceptible Populations: Models of Cancer Risk Prediction (Strom) Molecular Epidemiology of Hormonal-related Cancer	(Hanis) High throughput methods for genetic and molecular epidemiology
9, 11	Molecular Epidemiology of Infectious Disease (Hwang) HCV, HBV (Follen-Mitchell) HPV	Other study designs and methods: Case-Only designs, gene-environment studies Genomic techniques – microarrays and others
16, 18	(Lotan) Natural Agents in Cancer Prevention (Cinciripini) Genetic Susceptibility to nicotine addiction	(del Junco) Tying all the pieces together Developing collaborations
23, 25		**Discuss Lab Assignment #4: linkage analysis** Data presentation skills and time to work on projects
Apr. 30, May 2	Student presentations for molecular epi	**FINAL PROJECT DUE**

Appendix G

Adolescent Soyfood Intake, Insulin-Like Growth Factor-I and Breast Cancer Risk. *M. Sanderson, X.O. Shu, F. Jin, Q. Dai, H. Yu, Y.T. Gao, W. Zheng. (University of Texas School of Public Health at Brownsville, Brownsville, TX, 78520)

Previous reports from the Shanghai Breast Cancer Study (SBCS) suggested that adolescent and adult soyfood intake was inversely related to the risk of breast cancer, and elevated levels of insulin-like growth factor I (IGF-I) were associated with an increased risk of breast cancer. In the current study, we assessed whether IGF-I levels modified the effect of soyfood intake on breast cancer risk. The SBCS is a population-based case-control study of breast cancer among women age 25 to 64 conducted between 1996 and 1998 in urban Shanghai. In-person interviews were completed with 1459 incident breast cancer cases ascertained through a population-based cancer registry, and 1556 controls randomly selected from the general population in Shanghai (with respective response rates of 91% and 90%). This analysis is restricted to the 300 cases and 300 matched controls for whom information on IGF-I levels was available. After adjustment for confounding, the protective effect of soyfood intake was only observed among women with a lower IGF-I level (OR= 0.56 for adolescent and OR=0.68 for adult soyfood intake) but not for women with a higher IGF-I level (OR=1.41 for adolescent and OR=2.12 for adult soyfood intake), although none of the point estimates was statistically significant, possibly due to the small sample size. Higher IGF-I level was associated with an increased risk of breast cancer regardless of the level of soyfood intake. Our results appear to suggest that the effect of soyfood intake on breast cancer risk is dependent on adult IGF-I levels. Further studies are needed to confirm our finding and to understand the biological mechanism of this possible interaction.

Appendix H

DEPARTMENT OF THE ARMY
US ARMY MEDICAL RESEARCH ACQUISITION ACTIVITY
820 CHANDLER STREET
FORT DETRICK, MARYLAND 21702-5014

REPLY TO
ATTENTION OF:

May 29, 2002

Business Operations Division

Dr. Gerson Peltz
The University of Texas at Brownsville
Texas Southmost College
80 Fort Brown
Brownsville, TX 78520

RE: BC020061 - "Interrelationships of Hormones, Diet, Body Size, and Breast Cancer among Hispanic Women"

STATUS: INVITATION TO SUBMIT A FULL PROPOSAL AND PARTICIPATE IN A TELECONFERENCE

Dear Dr. Peltz:

On behalf of the Fiscal Year 2002 (FY02) Department of Defense Breast Cancer Research Program (BCRP) of the U.S. Army Medical Research and Materiel Command's Office of the Congressionally Directed Medical Research Programs (CDMRP), you are invited to submit a full Historically Black Colleges and Universities/Minority Institutions (HBCU/MI) Partnership Training Award proposal. This invitation to submit a full proposal was based on a screening process in which each pre-proposal was evaluated in accordance with the screening criteria published in Program Announcement I for the BCRP, released February 21, 2002. Your pre-proposal was screened by a multidisciplinary panel composed of BCRP Integration Panel members. The BCRP Integration Panel provided the following general information for the HBCU/MI Partnership Training Award during the pre-proposal review.

> In general, applicants submitting a full proposal to the HBCU/MI Partnership Training Award need to ensure that a team of investigators is identified at the mentor institution that are interested in training the investigators from the HBCU/MI. In cases where no more than two investigators were enrolled in the training program at the HBCU/MI, the proposal may be strengthened by the enrollment of additional investigators. A day-to-day mentoring and administration program that optimizes the collaboration between the institutions to develop a breast cancer-relevant training program should be fully described within the proposal. During preparation of the full proposal, the training environment should be fully described, and should include a description and qualifications of the people that will be trained at the HBCU/MI. The investigators should note that although the training of undergraduates in breast cancer research is an admirable aim for this training program, undergraduate training is not supported by this award mechanism. All applicants should be aware that full proposals for this mechanism will be reviewed according to the scientific peer review and programmatic review evaluation criteria for invited proposals found within the BCRP FY02 Program Announcement I.

In addition to the above-mentioned information regarding the HBCU/MI Partnership Training Award mechanism, the representatives of the CDMRP and the BCRP Integration Panel invite all individuals selected to send in a full HBCU/MI Partnership Training Award proposal to participate in a

teleconference. The teleconference will provide a forum for an interactive discussion about the intent and goals of the HBCU/MI Partnership Training Award mechanism. This meeting will include general feedback on how to further refine your submission and will provide an opportunity for you to ask questions. If interested in obtaining clarification on full proposal requirements, you or one of your collaborators are invited to participate in the teleconference. The teleconference has been scheduled for **June 6, 2002 from 9:30 to 11:00 a.m. Eastern Time.** The toll free number within the United States but outside of San Diego is 1-800-366-7242. When you call in, ask for pass code "33113," then press the pound (#) sign, or ask the operator for the Breast Cancer teleconference, chaired by Dr. Jane Mural.

A password will be sent to you via the e-mail address provided with your pre-proposal submission. This password will allow you to electronically submit your invited proposal at https://cdmrp.org/proposals.

Full proposals must meet all criteria and comply with preparation guidelines for HBCU/MI Partnership Training Award proposals as described in Program Announcement I for the BCRP, available on the web at http://cdmrp.army.mil/funding/02bcrp1.htm. Applicants should also refer to Program Announcement I for information on proposal review procedures, evaluation criteria, intent of the award mechanism, and other important information regarding proposal content.

Please note that this invitation to submit a full proposal is not an assurance of funding. Funding decisions will be made based on adherence of full proposals to the published criteria.

Sincerely,

Patricia A. Evans

Patricia A. Evans
Contracting/Grant Officer